REMARKS

Summary of the Office Action

Claims 6-26 and 33-38 are pending in the application, of which claims 6-15 and 34-38 are under examination. Claims 16-26 and 33 are withdrawn from consideration as being drawn to a non-elected invention.

Claims 6-15 and 34-38 are rejected as lacking enablement under 35 U.S.C. § 112, first paragraph, and claims 6, 10, 11, and 13-15 are rejected as lacking sufficient written description under 35 U.S.C. § 112, first paragraph.

Rejections Under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 6 and 9-15 are rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. According to the Examiner, the rejection is based upon the reasons of record, as set forth in a previous Office Action, issued 24 February 2003.

The Examiner states that "[T]he claims encompass delivery of biologically active molecules such as toxin polypeptides, which the skilled artisan would expect to require targeting to have therapeutic ability." (page 4 of Office Action.) The Examiner then acknowledges that some embodiments of the claimed invention would not require targeting selected cells for therapeutic effect, as demonstrated by the showings in the Declaration of Dr. Hawiger, but states that: "However, given that the claims are directed to methods of using widely divergent biologically active molecules, including molecules that would require targeting to selected cells to be used therapeutically, the showings of the Declaration do not support enablement for the full scope of the claimed invention."

The test of enablement, according to the MPEP section 2164.01, is "whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention." The Examiner is applying a different standard by requiring the specification to enable a limitation not found in the claim; namely, requiring some means to prevent importation of the molecule into all cells. Absent this limitation in the claim, the Examiner cannot require enablement for this limitation in the specification. Furthermore, the MPEP states "As long as the specification

discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of the 35 U.S.C. 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24, (CCPA 1970.)" (MPEP 2164.01(b).) As clearly shown by the Declaration of Dr. Hawiger previously provided, as well as the examples in the specification wherein the claimed invention has been reduced to practice, one of skill in the art would have been able to make and use the invention as claimed.

Applicants respectfully point out that avoiding systemic importation into all cells is *not* critical to the invention, nor does the specification state that such avoidance is critical to the invention. In fact, the specification merely states that "any selected cell into which import of a biologically active molecule would be useful can be targeted by this method, as long as there is a means to bring the complex in contact with the selected cell. Cells can be within a tissue or organ, for example, supplied by a blood vessel into which the complex is administered" (see Specification, page 14, lines 13-17). The specification goes on to state that the cells of the lung epithelium can be targeted by inhalation of the complexes, or the complexes can be administered directly to a target site in the body. The specification also states that signal peptides that are known to be utilized by the selected target cell can be used (see page 14, lines 17-28); however, nowhere does the specification state that such target-specific signal peptides *must* be used, and nowhere does the specification state that the complexes cannot be systemically delivered, or that certain types of cells must be avoided. Therefore, the statement that "avoiding systemic importation into all cells is critical" is not accurate. Moreover, as stated in the specification (see, e.g., page 8, line 2, through page 10, line 18), for *in vivo* administration, the peptides can be delivered by routine methods, e.g., parenterally, intravenously, by inhalation, by subcutaneous or intramuscular injection, by topical administration, by oral administration, etc.

In regard to the statement by the Examiner that "the claims encompass delivery of biologically active molecules such as toxin polypeptides, which the skilled artisan would expect to require targeting to have therapeutic ability." (page 4 of the Office Action.) The Examiner's concerns regarding the delivery of toxic polypeptides are not within the realm of concern of the Patent Office. According to the MPEP 2107.03, "[W]hile an applicant may on occasion need to provide evidence to show that an invention will work as claimed, it is improper for Office personnel to request evidence of safety in the treatment of humans, or regarding the degree of

effectiveness." The MPEP 2107.03 also states that "The Office must confine its review of patent applications to the statutory requirements of the patent law. Other agencies of the government have been assigned the responsibility of ensuring conformance to standards established by statute for the advertisement, use, sale or distribution of drugs." Regarding the enablement requirement, the Patent Office is responsible for ensuring that the one skilled in the pertinent art is able to make and use the claimed invention, not that it would have been safe in every conceivable application of it.

The Office Action also states that "Another aspect of the claimed method which must be addressed on a case-by-case basis is the operability of the cargo delivered by importation competent signal peptide." (Page 6). The Examiner goes on to say that "The specification teaches...since very large proteins are exported by cells...very large proteins can be imported into cells by this method... However, the accuracy of this assumption requires that the mechanism by which these large proteins are exported is the same mechanism by which hydrophobic importation competent signal peptides import proteins." (Page 6). The Examiner goes on to state that "Most large proteins are secreted by vesicular transport from the endoplasmic reticulum via the Golgi to the cell surface and fusion of the secretory vesicles with the plasma membrane." (Page 6). Applicants would like to point out that the molecules imported by the claimed methods pass through the membrane which is entirely analogous to proteins with signal peptides crossing the endoplasmic reticulum (ER) membrane. For at least this reason, the mechanism of subsequent processing and transport of proteins after crossing the ER membrane are not relevant to the claimed importation into cells. The claimed signal peptides allow transport across a membrane (cell membrane or ER membrane) and, as is know form the many proteins transported across the ER membrane, a wide size range of proteins can be so transported. There is no evidence presented in the Office Action to the contrary. As the Examiner pointed out, "...hydrophobic importation polypeptides...ferry their cargo through the plasma membrane directly, absent endocytosis." This is correct and describes the nature of the analogous transport of proteins across the ER membrane which supports the operability of the claimed methods. The statement made above that because large proteins can be exported that they can also be imported was simply made to indicate that the size of cargo that to be imported

can vary as much as the size of the cargo to be exported, as the signal sequence is used to both allow the exportation and importation of molecules.

The Examiner also quotes Applicant's own publication (Veach *et al.* (2004) *J. Biol. Chem.* 279:11425-31), specifically the statement that "[t]he plasma membrane imposes tight control on the access of extracellular peptides and proteins to the cell interior." However, this passage was mischaracterized. Veach *et al.* goes on to say: "To bypass these inherent mainstays of the plasma membrane functional integrity, we harnessed a signal-sequence derived hydrophobic region to deliver functional cargoes composed of peptides and proteins to probe and modulate intracellular signaling." (p. 11425, bridging cols.) Therefore, the Applicants have found that the plasma membrane can be bypassed with the use of a signal sequence, which allows for the importation of biologically active molecules.

The Examiner then goes on to state that "...one of ordinary skill in the art would not expect the ability of hydrophobic importation polypeptide fusion protein to cross the plasma membrane to be independent of the cargo peptide, polypeptide or protein comprised within the fusion protein." (Page 7). However, the hydrophobic importation polypeptide fusion protein does not cross the plasma membrane independently of the cargo peptide, but rather allows for it's importation into the cell. The Examiner cites Namiki *et al.*, which showed that the transduction of GST was independent of the signal-sequence-based peptide. However, this was because GST itself was found to have a protein transduction domain, thereby not requiring a signal sequence for importation. The fact that GST was able to transduce without a signal sequence-based peptide is not a general characteristic of cargo peptides, but a specific statement regarding GST, and that GST itself is capable of transduction, and is therefore not in need of a signal sequence.

The Examiner states that "the teachings from the art and specification clearly do not provide sufficient guidance with regard to which cargo proteins, peptides, or polypeptides can be delivered into a cell *in vivo* such that the skilled artisan could practice the broad claims without undue experimentation." (Page 7 of the Office Action). However, as the MPEP states, "If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied." As the Examiner has acknowledged, the specification teaches how to use the invention as claimed. Specifically, the specification states that "Therefore, size ranges for

proteins from a few amino acids to around a thousand amino acids can be used. A preferable size range for proteins is from a few amino acids to about 250 amino acids." (Specification, page 6.) Specific ranges of molecular weights of these proteins are also given in the specification. Therefore, the requirement that the specification recite how to use the claimed invention is clearly met.

The MPEP states "[p]roof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation." (MPEP 2164.02). The Examiner cited Lindgren *et al.* and Namiki *et al.* to show that cell-penetrating peptides were not known in the art for large cargoes, and therefore the art does not provide sufficient guidance for their importation. However, the present invention uses hydrophobic importation competent signal peptides, which were not used in the art at the time of the invention. Hydrophobic importation signals are able to translocate large cargo across the membrane of endoplasmic reticulum in protein seretory pathways. Hence, using this sequence for delivery of "large cargo" into cells is predicated on the same function as signal sequences. The Applicants have provided sufficient evidence and disclosure to show that these signal peptides would have been capable of importing proteins that range in size up to about a thousand amino acids, as recited in the instant specification.

The Examiner has also argued that undue experimentation would be required to practice the method using the broad scope encompassed by the importation competent signal peptide of the claims. The Examiner also states that the Applicant's arguments regarding routine experimentation aren't persuasive because they fail to take into account the tremendous number of peptides that would have to be assayed for activity, stating that this could encompass millions of peptides. However, Applicants would like to point out that not every peptide would need to be assayed for activity, as only those which are hydrophobic importation competent signal peptides are claimed. As the specification states, "Signal peptides can be selected, for example from the SIGPEP database, which also lists the origin of the signal peptide. When a specific cell type is to be targeted, a signal peptide used by that cell type can be chosen." (Page 11.) Therefore, the SIGPEP database, which would have been well known to those of skill in the art at the time of the invention, could have been used to make and use the invention as claimed. Moreover, any

selected signal peptide can be tested for its ability to function as an importation competent signal peptide, using routine screening methods that employ the *in vitro*, *ex vitro*, and *in vivo* teachings set forth throughout the entire specification, including the Examples, together with what was already known in the art. Accordingly, identification of additional importation competent signal peptides is *routine experimentation*, not undue experimentation, and the present methods, as claimed herein, are fully enabled in this regard.

Rejections Under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 6, 10, 11, and 13-15 are rejected under 35 U.S.C. § 112, first paragraph, as lacking sufficient written description. The Office Action asserts that Applicants did not have possession of the entire genus of importation competent signal peptides, but only a method for how to identify an importation competent signal peptide experimentally. Applicants respectfully traverse.

In response to Applicant's previous arguments, the Examiner cites the Applicant's own work (Veach *et al.*) and states that "In the publication Applicant suggests that there is a proline residue comprised within hydrophobic importation polypeptides that is critical to their ability to cross the plasma membrane" (p. 11). However, Veach *et al.* did not construe the presence of the proline to be "critical," unlike the Examiner's characterization. In fact, Veach *et al.* simply stated that the hydrophobic region contained a proline, and stated that the presence of proline "may allow SSHR to form, within a phospholipid bilayer, a hairpin-like loop that constitutes a leading edge for the attached cargo." (page 11430.) Veach *et al.* goes on to postulate another reason for the ability of SSHR to pass through the phospholipid bilayer: a "tilted peptide" translocation mechanism. Therefore, the Examiner's characterization that the proline is "critical" is inaccurate, as the paper clearly shows that there are several possible mechanisms that are not mutually exclusive. Furthermore, another publication by the inventor (Liu et al., Proc. Natl. Acad. Sci. USA Vol. 93, pp. 11819–11824, October 1996) states that, "The cell-permeable peptides were designed by using the hydrophobic region Val-Thr-Val-Leu-Ala-Leu-Gly-Ala-Leu-Ala-Gly-Val-Gly-Val-Gly of the signal peptide sequence of human integrin b3 followed by the sequences of the cytoplasmic segments..." (page 11819). Therefore, the characterization that a proline residue is necessary is unfounded based on the above, in which no proline is found in the signal peptide.

The first paragraph of 35 U.S.C. § 112 requires "a written description of the *invention*." The invention here is a method including a single step, i.e., administering to the subject a complex comprising a peptide, polypeptide, or protein linked to a mammalian hydrophobic importation competent signal peptide. Thus, written description of the claimed method requires description only of the act to be performed because the act to be performed in the claimed method is what the invention is. Nothing in the statute or the case law requires a written description of anything other than the *claimed invention* for compliance with the written description requirement. As an aside, and as discussed in detail hereinabove, Applicants note that whether those of skill in the art can succeed in carrying out the acts of the method and achieve the claimed results is solely a question of enablement.

As previously discussed, the specification provides a description of the method step. Applicants submit that the step of administering to a subject a peptide, polypeptide, or protein linked to an importation competent signal peptide is adequately described in the specification (e.g., at page 8, line 2, through page 10, line 18). For at least these reasons, Applicants asserts that the claimed method is adequately described.

As stated above, the claimed methods only require administration to a subject of a peptide, polypeptide, or protein linked to a mammalian hydrophobic importation competent signal peptide, and, Applicants submit, only requires written description of the method step (that is, administration). Applicants assert that the other aspect of the claimed method (i.e., importation competent signal peptides to be used in the claimed method) implicates only the enablement requirement of 35 U.S.C. § 112, first paragraph, because they involve not the claimed method itself, but rather how to make and use the claimed method.

Furthermore, as discussed above, the written description requirement and enablement requirement are distinct requirements based on different clauses of 35 U.S.C. § 112, first paragraph. In particular, the requirement of a description of the manner of making and using the claimed method is not a part of the written description requirement. Thus, features of the claimed method that involve how to make and use the method need not be described according to the requirements of written description. The claim requires that the peptide, polypeptide, or protein be imported into the cell of the subject. This is an *effect* of the method, not a step of the method. Obtaining this effect is solely an issue of enablement, not written description. The

effect is not a step or act required to perform the method, it is only a result that those of skill in the art must be able to *obtain* (without the need for undue experimentation) *when* they practice the claimed method (that is, *when they perform the step* of the method). Those of skill in the art must practice the method so as to obtain the claimed effect. This is a feature of the *use* of the claimed method, not of the method step *per se*, and as such, is only a feature of how to use the claimed method. Because how to use the claimed method is not a part of the written description requirement, such use is not a proper area of inquiry in assessing written description of the claimed method.

In response to the arguments above, the Examiner stated that "a description of a method of using a product must describe the product being used in order to meet the written description requirement." (Page 12). However, such a product has been described in the specification. Specifically, the specification gives the Example of SN50 (page 29) as well as many other signal peptides: "Signal peptides can be selected, for example from the SIGPEP database, which also lists the origin of the signal peptide. When a specific cell type is to be targeted, a signal peptide used by that cell type can be chosen." (Page 11.) The SIGPEP database (http://proline.bic.nus.edu.sg/sigpep/) is a signal peptide database containing signal/leader sequences of prokaryotes and eukaryotes, and was known to those of skill in the art at the time of the invention. The sequences of the database are stored in MySQL relational database and provided as DNA and protein sequences. Therefore, the written description requirement is met, in that the Applicant has clearly shown possession of the importation competent signal peptides.

Furthermore, in regard to *Enzo Biochem. V. Gen-Probe*, 296 F.3d 1316 (Fed. Cir. 2002), the Examiner states "Thus, the court clearly indicates that, contrary to Applicant's assertion, a recitation of functional characteristics alone does not provide adequate written description for a molecule. Instead, the statements made in *Enzo* and the Written Description Guidelines, when viewed in context, provide that a recitation of function must be 'coupled with a known or disclosed correlation between function and structure.'" (Page 11 of the Office Action.) However, the signal peptides of the instant claims are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend, and therefore the Examiner's arguments are inapposite to both *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559 (Fed. Cir. 1997) and *Enzo. Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 65 U.S.P.Q.2D (BNA) 1385,

1332 (Fed. Cir. 2003). In *Amgen*, the claims of Amgen's patents referred to types of cells that can be used to produce recombinant human EPO. TKT (Amgen's opponent) argued that, because the Amgen patents did not describe the structure of the claimed cells, the patents failed to provide adequate written description of the claimed subject matter as required by *Eli Lilly* and *Enzo*. The court in Amgen rejected this argument, holding that Amgen's claims, including the recited cells, were adequately described in Amgen's patents. The court noted that unlike in *Eli Lilly* or *Enzo* "the claim terms at issue here [in *Amgen*] are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend....This difference alone sufficiently distinguishes Eli Lilly, because when used, as here, merely to identify types of cells (instead of undescribed, previously unknown DNA sequences), the words 'vertebrate' and 'mammalian' readily 'convey distinguishing information concerning [their] identity' such that one of ordinary skill in the art could 'visualize or recognize the identify of the members of the genus.'" Like the cells of *Amgen*, the claimed importation competent signal peptides are well known biological materials; well classified and easily recognized by those of skill in the art. As a result, and as in *Amgen*, the present application satisfies the written description requirement for the present claims. Applicants therefore respectfully request the removal of this rejection.

In view of the above, the specification provides sufficient description of pending claims 6, 10, 11, and 13-15, and this basis of the written description rejection can be withdrawn.

CONCLUSION

In view of the above amendments and remarks, reconsideration and allowance of the pending claims is believed to be warranted, and such action is respectfully requested. The Examiner is encouraged to directly contact the undersigned if this might facilitate the prosecution of this application to issuance.

A Credit Card Form PTO-2038 authorizing payment in the amount of $510.00 representing the fee for a small entity under 37 C.F.R. § 1.17(a)(3) and a Request for Extension of Time are enclosed. No additional fees are believed due. However, the Commissioner is hereby authorized to charge any deficiency or to credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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Janell T. Cleveland — March 17, 2005
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